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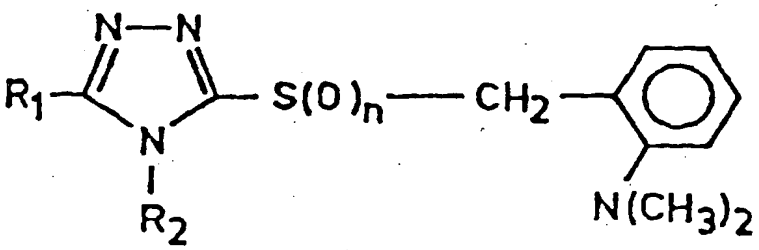
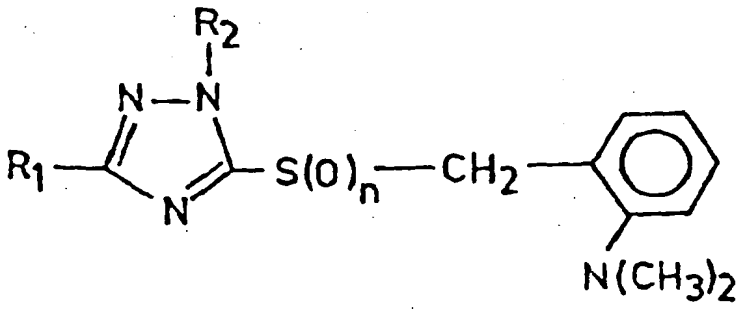
(54) Title: ULCER-INHIBITING TRIAZOLE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME

(57) Abstract

The invention relates to novel 1,2,4-triazole derivatives of formulae (Ia) and (Ib), wherein R_1 and R_2, which are the same or different, stand for hydrogen; C_{1-4} alkyl or C_{1-4} alkenyl group; or a phenyl group optionally substituted by C_{1-4} alkyl or alkoxy group; and n is 0, 1 or 2, and acid-addition salts of these compounds. The invention further relates to pharmaceutical compositions containing these compounds as well as a process for the preparation of the compounds of formulae (Ia) and (Ib). The compounds of formulae (Ia) and (Ib) inhibit gastric-acid secretion and exert a significant protective effect on the gastric mucosa (cytoprotective action). Thus, they can be used for inhibiting and treating ulcers of the digestive system.



(Ia)



(Ib)

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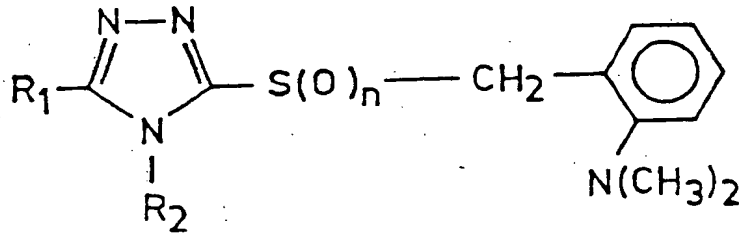
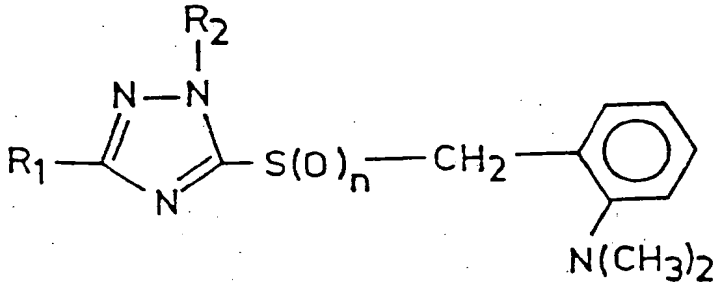
ULCER-INHIBITING TRIAZOLE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME

This invention relates to novel 1,2,4-triazole derivatives of formulae (Ia)



(Ia)

and (Ib),



(Ib)

wherein

R_1 and R_2, which are the same or different, stand for hydrogen; C_{1-4} alkyl or C_{1-4} alkenyl group; or a phenyl group optionally substituted by C_{1-4} alkyl or alkoxy group; and

n is 0, 1 or 2,

as well as their acid-addition salts and pharmaceutical compositions containing these compounds.

According to an other aspect of the invention there is provided a process for the preparation of new compounds of general formulae (Ia) and (Ib) as well as acid-addition salts thereof.

The novel triazole derivatives of general formulae

(Ia) and (Ib) of the invention possess valuable pharmacological effects. Namely, they inhibit the gastric acid secretion, moreover they exert a significant protective effect on the gastric mucose (cytoprotective action). Thus, they can very preferably be used as active agents of medicaments against ulcer of the digestive system.

The invention relates also to a method of treatment, which comprises administering a therapeutically effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable acid-addition salt thereof into the organism of a patient for protecting the gastric mucose or against ulcers of the digestive system.

In a preferable group of the compounds of general formulae (Ia) and (Ib) of the invention R_1 means hydrogen or methyl group, R_2 stands for a methyl group and n is 0 or 1.

The following compounds are especially preferred:

3-{[2-(dimethylamino)benzyl]sulfinyl}-4,5-dimethyl--1,2,4-triazole,

3-{[2-(dimethylamino)benzyl]thio}-4,5-dimethyl--1,2,4-triazole,

3-{[2-(dimethylamino)benzyl]thio}-2-methyl-1,2,4--triazole,

3-{[2-(dimethylamino)benzyl]thio}-2,5-dimethyl--1,2,4-triazole,

and the acid addition salts of these compounds.

It is known that compounds inhibiting gastric-acid secretion bear the highest importance in the treatment of ulcers of the digestive system. One type of these compounds is represented by the histamine-2-receptor--blocking agents (such as e.g. cimetidine and ranitidine); whereas an other type of these compounds involves substances acting by inhibition of the H^+/K^+-ATP-ase enzyme.

The major part of gastric acid secretion-inhibiting

compounds of the latter type are benzimidazole derivatives discussed e.g. in the published European patent applications Nos. 0,005,129 and 0,204,215 as well as in the United States patent specifications Nos. 4,045,564, 4,359,465, and 4,472,409. From these compounds, 2-{[3,5--dimethyl-4-methoxypyridin-2-yl)methyl]sulfinyl}-5--methoxy-1H-benzimidazole has been recently introduced to therapy.

Gastric acid secretion-inhibiting pyrimidinone derivatives are described in the published Japanese patent applications Nos. 60-228,465 and 60-197,673 as well as in the Hungarian patent specification No. 203,736.

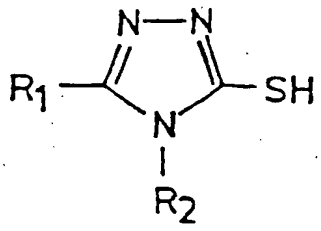
Among the compounds having similar effect, imidazole derivatives fused with various heterocycles (e.g. in the published European patent applications Nos. 0,234,485 and 0,234,690), substituted oxazole, thiazole and imidazole derivatives (in the published European patent application No. 0,262,845) as well as imidazole, triazole and tetrazole derivatives (in the published Japanese patent application No. 62-207,270) have also been disclosed. However, the triazole derivatives published in the last-mentioned literature reference can well be distinguished from the compounds of general formulae (Ia) and (Ib) of the present invention.

The aim of the present invention is to prepare compounds, the gastric acid secretion-inhibiting effect of which reaches or exceeds that of active substances of the prior art without adverse side-effects and which exert a significant cytoprotective action, too.

It has been found during our investigations that the compounds of the invention, which are structurally different from the gastric acid secretion-inhibiting substances known in the art, entirely satisfy the above demands.

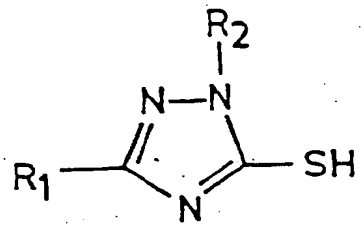
Furthermore, it has surprisingly been found that

compounds of general formulae (Ia) and (Ib) of the invention, wherein R_1 and R_2 are as defined above and n is zero, can be prepared in excellent yield and high purity in such a way that, contrary to the usual S-alkylation, a 1,2,4-triazolethiol of general formula (IIa)



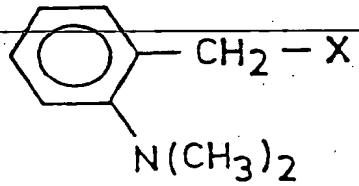
(IIa)

or (IIb),



(IIb)

respectively, wherein R_1 and R_2 are as defined above, or a tautomer thereof is reacted with a compound of general formula (III),



(III)

wherein X stands for a leaving group, or with an acid-addition salt thereof without using any base.

Thus, according to the present invention, the 1,2,4-triazole derivatives of general formulae (Ia) and

(Ib), wherein R_1, R_2 and n are as defined above, and their acid-additon salts can be prepared by reacting a compound of general formula (IIa) or (IIb), respectively, wherein R_1 and R_2 are as defined above, or a tautomer thereof with a compound of general formula (III), wherein X means a leaving group, or with an acid-addition salt thereof and, if desired, transforming an obtained compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is zero, to a compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is 1 or 2, by oxidation and optionally by subsequent reduction and/or converting an obtained base to an acid-addition salt by using an organic or inorganic acid or converting an obtained salt to the corresponding free base.

According to the definition accepted in the literature [T. A. Geissman: Principles of Organic Chemistry, 3rd ed., ed. W. H. Freeman, London (1968)] the leaving group X is meant to be a group which can easily be split by a nucleophilic reagent. Such groups are the halogen atoms, especially chlorine, bromine and iodine; as well as sulfonyloxy groups, e.g. the lower alkylsulfonyloxy and optionally substituted benzenesulfonyloxy or toluenesulfonyloxy groups.

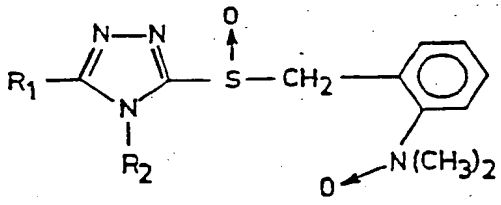
According to a preferred embodiment of the process of the invention the starting substances [of which the compound of general formula (III) is preferably used in the form of an acid-addition salt] are dissolved in a dipolar aprotic solvent, preferably N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide or acetonitrile, and then the components are reacted in a homogeneous solution at a temperature between 10 °C and 60 °C, suitably between 20 °C and 40 °C. The duration of the reaction varies from 5 minutes to 24 hours depending on the reagents used. The compounds of general formulae

(Ia) and (Ib), wherein R_1 and R_2 are as defined above and n is zero, formed in the alkylation reaction are separated as acid-addition salts or preferably in the base form after liberation by aqueous sodium hydrogen carbonate solution and extraction into a halogenated hydrocarbon, preferably methylene chloride or chloroform.

According to the invention, in order to prepare compounds of the general formulae (Ia) and (Ib), wherein R_1 and R_2 are as defined above and n is 1 or 2, a compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is zero, obtained in the above-described alkylation reaction is treated with an oxidizing agent suitable to oxidize the S atom of the molecule to a sulfinyl or sulfonyl group, respectively. The transformation of this type can be accomplished by a number of reagents known in the literature. It is advantageous to use 3-chloroperbenzoic acid, tert-butyl hydroperoxide, sodium hypochlorite or hydrogen peroxide in the presence of metal ions. The use of 3-chloroperbenzoic acid is particularly preferred. Furthermore, it is suitable to employ the oxidizing agent in a small, preferably 0.1 to 0.4 equivalent, excess. The reaction can be carried out in organic solvents, preferably halogenated hydrocarbons at room temperature. When necessary, the final product preferably separated in the base form can be purified by recrystallization or column chromatography, suitably by using silica gel.

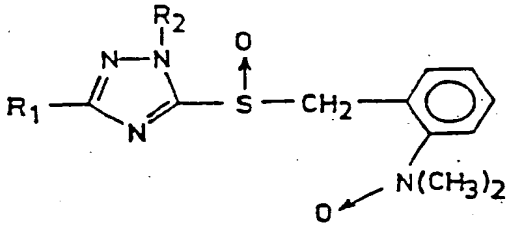
According to the invention compounds of the general formula (Ia) or (Ib), wherein R_1 and R_2 are as defined above and n is 1, can alternatively preferably be prepared by oxidizing a compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is zero, obtained in the alkylating reaction, in an organic solvent, preferably in a halogenated hydrocarbon, at room temperature by using 3-chloroperbenzoic

acid in an excess of 0.5 to 0.8 equivalent. In this case a mixed oxidation product is obtained which consists mainly of an N-oxide type intermediate of general formula (IVa)



(IVa)

or (IVb),



(IVb)

respectively, wherein R_1 and R_2 are as defined above, and of a small amount of a compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is 1. It has been recognized that the part of the reaction mixture consisting of the compound of general formula (IVa) or (IVb), respectively, can also be transformed to the desired sulfinyl compound (n = 1) of general formula (Ia) or (Ib), respectively, in such a manner that, after termination of the oxidizing reaction, the N-oxide of general formula (IVa) or (IVb), respectively, is extracted with water from the halogenated hydrocarbon used and then it is reduced by using sulfurous acid in an aqueous solution. The reduction by sulfurous acid may be carried out either in the separated aqueous solution or in the heterogeneous reaction mixture containing the halogenated hydrocarbon and water. In the

first case the sulfinyl compound of general formula (Ia) or (Ib), respectively, obtained by the reduction is recovered from the aqueous solution after alkalinization by extracting it with a halogenated hydrocarbon. After combining the extract obtained with the halogenated hydrocarbon solution arising from the original reaction mixture and evaporating it, the desired sulfinyl compound is obtained which is then purified, when necessary, by recrystallization.

In the reduction carried out in a heterogeneous system the halogenated hydrocarbon solution containing the sulfinyl compound of general formula (Ia) or (Ib), respectively, is directly obtained and then worked up as described above.

In the above-described combined reaction route (including both oxidation and reducing steps) sulfinyl compounds with a suitable quality can be obtained without purification by column chromatography, too.

The compounds of general formulae (Ia) and (Ib) of the invention can be converted to acid-addition salts by using commonly known and employed processes or, if in the process according to the invention salts are obtained, if desired, the corresponding bases can be liberated.

The starting substances of the process according to the invention are usually known and commercially available; or they can be prepared from easily available basic materials by using known methods.

As mentioned in the introduction, the compounds of general formulae (Ia) and (Ib), werein R_1, R_2 and n are as defined in the introductory part, possess significant in vivo gastric acid secretion-inhibiting and cytoprotective effect.

The gastric acid secretion-inhibiting, ulcer-inhibiting and cytoprotective effects of the compounds of general formulae (Ia) and (Ib) were proven by investiga-

tions under in vivo conditions by using the methods described hereinafter under items 2 to 4. The compound 2--{[2-(dimethylamino)benzyl]sulfinyl}-1,4-benzimidazole [Drugs of the Future 13, 186 (1988); hereinafter compound NC-1300] and omeprazole (see the published European patent application No. 0,005,129) were used as reference drugs.

The fact that the compounds of general formulae (Ia) and (Ib) of the invention exert their above-mentioned effects by inhibiting the H^+/K^+-ATP-ase enzyme, was supported by in vivo investigations described below under item 1, wherein omeprazole was used as reference drug.

1. Assay of the H^+/K^+-ATP-ase enzyme inhibition

The H^+/K^+-ATP-ase enzyme was prepared by using the modified method of H. Chang et al. [Biochim. Biophys. Acta 464, 313-327 (1977)] on swine gastric mucosa. A G_2 fraction purified on sugar gradient was used in these measurements. The enzyme activity was measured in 1 ml volume of the reaction mixture containing 2 mM of $MgCl_2$, 2 mM of ATP, 20 mM of potassium chloride and enzyme in 40 mM of TRIS acetate (pH = 7.4) buffer solution. The activity of Mg^{++}-ATP-ase enzyme was measured in the absence of potassium chloride. The H^+/K^+-ATP-ase enzyme activity was obtained as the difference between these two values.

Table 1

Assay of inhibition of the H^+/K^+-ATP-ase enzyme

Compound (Example No.)	Concentration (μM)	H^+/K^+-ATP-ase (μmol of ATP/mg of protein/hour)			
		Preparation 1		Preparation 2	
		X±SD	Inhibition %	X±SD	Inhibition %
Baseline		50.4±0.5		55.4±1.1	
15	100	4.1±1.3	91		
15	50	14.1±1.8	72	4.4±2.2	92

Table 1 (continued)

Compound (Example No.)	Concentration (μM)	H^+/K^+-ATP-ase (μmol of ATP/mg of protein/hour)			
		Preparation 1		Preparation 2	
		X±SD	Inhibition %	X±SD	Inhibition %
15	25	34.2±0.2	32	28.6±2.5	48
15	10	50.2±0.8	0	45.8±0.1	17
15	5			54.1±3.8	2
		IC_{50}: 34μM		IC_{50}: 21 μM	
Baseline		63.5±1.5			
17	100	11.5±2.7	82		
17	50	24.5±4.6	61		
17	25	31.3±5.9	51		
17	10	39.5±6.6	38		
17	5	44.3±5.1	30		
		IC_{50}: 19μM			
Baseline		63.5±1.5			
18	100	2.2±0.3	96		
18	50	2.8±0.8	95		
18	25	6.0±1.1	90		
18	10	22.1±7.5	65		
18	5	37.8±6.0	40		
		IC_{50}: 6.6 μM			
Baseline		43.4±3.2		31.7±2.2	
21	100	4.4±1.4	90		
21	50	8.9±1.8	80	2.9±1.8	91
21	25	15.1±2.9	65	7.2±2.0	77
21	10	22.1±3.0	50	12.8±1.6	59
21	5			17.7±1.6	44
21	1			32.7±5.3	0
		IC_{50}: 10μM		IC_{50}: 12 μM	
Baseline		106.7±1.2			
Omeprazole	100	4.5±2.8	96		
Omeprazole	50	5.1±0.4	95		
Omeprazole	25	21.7±4.2	80		
Omeprazole	10	57.5±2.4	46		
		IC_{50}: 10.7 μM			

n = 3

On the basis of the data of Table 1 it can be stated that the compounds described in Examples 18 and 21 are the most effective inhibitors of the H^+/K^+-ATP-ase enzyme. The average IC_{50} values of these compounds measured on two preparations are 6.6 μM and 8.5 μM, respectively, which are better than that of omeprazole (IC_{50} = 10.7 μM) used as reference drug.

2. Determination of the gastric acid secretion-inhibiting effect by using Shay's method

After 24-hour starvation female SPRD rats weighing 130 to 160 g each were orally treated with the compounds to be tested. Ten animals were used for each dose. After 1 hour laparotomy and pylorus ligation were carried out under ether anaesthesia according to Shay [Gastroenterology 5, 43 (1945)]. After 5 hours the animals were killed by an overdose of ether, their stomach was removed and the volume and acid content of the gastric juice were determined. Sodium hydroxide solution (0.1 N) was used for titration in the presence of Töpfer's indicator. The results are summarized in Table 2.

Table 2

Assay of inhibition of gastric acid secretion by using Shay's method

Compound Example No.	Dose mg/kg p.o.	Gastric juice (ml) Control	Treated	Change %	Gastric acid (ml) Control	Treated	Change %	ED_{50} mg/kg p.o.
5	2.5	7.22	7.32	+ 1	3.70	3.14	-15	6.3
	5.0	7.22	6.31	-13	3.70	2.86	-23	(4.0-9.9)
	10.0	5.36	3.87	-28	3.03	0.74	-76	
6	2.5	9.36	8.68	- 3	5.50	4.21	-23	5.0
	5.0	9.20	6.08	-34	4.52	3.09	-32	(3.4-7.5)
	10.0	9.36	4.54	-51	5.50	1.13	-79	

Table 2 (continued)

Compound Example No.	Dose mg/kg p.o.	Gastric juice (ml) Control	Gastric juice (ml) Treated	Change %	Gastric acid (ml) Control	Gastric acid (ml) Treated	Change %	ED_{50} mg/kg p.o.
7	5.0	8.35	9.79	+17	4.91	3.33	-32	7.5
	10.0	9.62	5.55	-42	4.08	1.57	-62	(4.5-12.3)
	20.0	10.13	3.82	-62	4.69	0.48	-90	
9	1.25	8.71	7.55	-13	4.50	4.11	-10	4.4
	2.5	11.37	8.17	-28	6.18	4.11	-33	(2.7-7.3)
	5.0	11.37	6.38	-44	6.18	2.89	-53	
	10.0	10.82	4.73	-56	5.75	1.26	-78	
15	2.5	8.71	6.48	-26	4.56	3.00	-33	5.2
	5.0	10.45	7.19	-31	5.44	2.76	-49	(2.9-9.3)
	10.0	10.35	5.94	-43	5.22	2.00	-62	
	20.0	9.19	4.42	-52	3.63	0.59	-84	
21	5.0	9.61	8.39	-13	4.92	3.14	-36	9.0
	10.0	10.13	6.44	-36	4.69	2.07	-56	(4.2-19.3)
	20.0	10.13	6.20	-39	4.69	1.62	-66	
Reference	10.0	7.30	6.11	-16	4.15	2.74	-34	16.0
drug	20.0	5.61	4.63	-18	3.25	1.36	-58	(11.9-21.4)
(NC-1300)	50.0	5.90	4.50	-24	3.43	0.41	-88	
Reference	5.0	6.88	5.40	-22	2.71	1.75	-35	10.5
drug	10.0	6.88	5.47	-22	2.71	1.70	-38	(7.8-14.1)
(Omeprazol)	20.0	6.98	4.30	-38	2.81	0.71	-75	

It can be seen from Table 2 illustrating the "spontaneous" gastric acid secretion-inhibiting effect of the novel triazole derivatives of the invention that the

compounds of Examples 5, 6, 7, 9, 15 and 21 proved to be significantly more active than the reference drugs.

3. Study on the cytoprotective effect

The modified method of Robert [Gastroenterology 77, page 761 (1979)] was used in these experiments. Twelve animals were used for each dose. The necrotizing agent (containing absolute alcohol and concentrated HCl in a ratio of 100 ml/2 ml) was orally administered in a final volume of 0.5 ml/100 g of body-weight 30 minutes following administration of the compound to be tested. After 1 hour the animals were killed by an overdose of ether and the size of necrosis appearing on the glandular part of their stomach was evaluated. The results are illustrated in Table 3.

Table 3

Investigation of cytoprotective effect

Compound Example No.	Dose mg/kg p.o.	Average length (mm) of the bleedings Control	Treated	Change %	ED_{50} mg/kg p.o.
5	5.0	77.9	56.1	-28	8.5
	10.0	67.4	30.8	-54	(5.2-13.8)
	20.0	67.4	9.8	-85	
13	5.0	76.6	67.2	-12	14.1
	10.0	76.6	57.8	-25	(8.9-22.4)
	20.0	80.3	23.4	-71	
Reference drug NC-1300	5.0	107.7	84.4	-22	8.6
	10.0	107.7	42.3	-61	(6.8-10.9)
	20.0	88.0	11.7	-87	
Reference drug (Omeprazol)	5.0	84.8	61.8	-27	10.0
	10.0	84.8	46.0	-46	(7.7-13.0)

It is obvious from the data of Table 3 that the compounds of Examples 5 and 13 inhibited in a dose-dependent manner the stomach-wall necrosis induced by absolute alcohol containing hydrochloric acid. Thus, these compounds possess a favourable cytoprotective effect.

4. Assay of the ulcer-inhibiting effect

a) Stomach ulcer-inhibiting effect on rats operat d according to Shay ("Shay rats")

These investigations were carried out on female SPRD rats weighing 150 to 170 g each after starvation for 24 hours. The animals were orally treated with a 20 mg/kg dose of the compounds to be tested in a final volume of 0.5 ml/100 g of body-weight. Then, after 1 hour laparotomy and pylorus ligation were performed under ether anaesthesia according to Shay [Gastroenterology 5, 43 (1945)]. After 18 hours the number and size of ulcers developed on the membraneous part of the stomach were evaluated under a stereomicroscope by using 8-fold magnification. The size of ulcers was expressed as a score from 0.5 up to 32. The score values of the treated group were compared to those of the group pretreated with the vehicle and expressed as percentage. The results are summarized in Table 4.

Table 4

Stomach ulcer-inhibiting effect on Shay rats

Compound Example No.	ED_{50} values (mg/kg p.o.) according to		
	number	severity of the ulcers	occurrence
1	5.0 (3.7-6.6)	4.3 (3.2-5.7)	4.7 (3.1-7.2)
5	6.1 (4.3-8.7)	6.6 (4.5-9.8)	13.2 (9.9-17.6)
15	7.0 (5.0-9.7)	4.3 (2.8-6.5)	12.3 (8.8-17.3)

Table 4 (contd.)

Compound Example No.	ED_{50} values (mg/kg p.o.) according to number of the ulcers	severity of the ulcers	occurrence
Reference drug NC-1300	7.4 (6.3-8.7)	5.7 (4.7-7.0)	14.5 (13.4-15.7)
Reference drug Omeprazole	9.2 (7.0-12.1)	11.0 (8.9-13.5)	17.0 (11.7-24.7)

b) Inhibition of reserpine-induced stomach ulcer

After starvation for 24 hours female SPRD rats were orally treated with a dose of 5 mg/kg and 20 mg/kg, respectively, of the compounds to be tested. Then, the rats were immediately treated with a 5 mg/kg subcutaneous dose of reserpine. After 18 hours the stomach of the animals was observed under microscope. The evaluation was carried out as described under paragraph a). The results are indicated in Table 5.

Table 5

Inhibition of reserpine-induced stomach ulcer

Compound Example No.	ED_{50} values (mg/kg p.o.) based on number of the ulcers	severity of the ulcers	occurrence
1	9.3 (6.6-13.0)	9.2 (6.6-12.9)	10 - 20
5	19.8 (14.3-27.5)	21.4 (16.1-28.3)	37.7 (24.8-57.4)
15	2.8 (1.9- 4.2)	2.6 (1.5- 4.3)	5.8 (3.8- 8.7)
Reference drug (NC-1300)	17.0 (12.4-23.3)	20.0 (16.5-24.2)	24.0 (19.4-29.8)
Reference drug (Omeprazole)	8.0 (5.6-11.4)	6.1 (4.1- 9.1)	18.0 (13.3-24.3)

c) Inhibition of indomethacin-induced stomach ulcer

These experiments were carried out on female SPRD rats previously starved for 24 hours. During this period the animals were allowed to drink water ad libitum. The animals were orally treated with a dose of 5 mg/kg and 20 mg/kg, respectively, of the compounds to be tested in a final volume of 0.5 ml/100 g, then after 1 hour they were orally treated with a 20 mg/kg dose of indomethacin in the same volume. After 6 hours the rats were killed by an overdose of ether and the ulcers developed on the glandular part of their stomach were examined as described in paragraph a) above. The results are summarized in Table 6.

Table 6

Inhibition of indomethacin-induced stomach ulcer

Compound Example No.	ED_{50} values (mg/kg p.o.) based on number of the ulcers	severity of the ulcers	occurrence
1	17.8 (14.9-21.1)	17.2 (13.4-22.0)	27.6 (19.8-38.5)
5	8.6 (5.4-13.6)	8.7 (6.0-12.8)	11.7 (7.2-18.9)
15	6.6 (4.4- 9.9)	7.7 (5.5-10.8)	10 - 20

It can be seen from Tables 4 to 6 that oral doses of 20 mg/kg of the compounds of the invention described in Examples 1, 5 and 15 effectively inhibited the development of stomach ulcer in rats by using various experimental models.

5. Acute toxicity investigations on mice and rats

These investigations were carried out on male CFLP mice and female SPRD rats previously starved for 24 hours. The animals were orally treated with various doses of the compounds to be tested. The observation period lasted 14 days. The results are summarized in Table 7.

Table 7

Investigation of the acute toxicity on mice and rats

Compound Example No.	Male mice Dose mg/kg p.o.	Died/ /treated	LD_{50}	Female rats Dose mg/kg p.o.	Died/ /treated	LD_{50}
1	1000	0/3		500	0/8	
	1500	2/3	1000-1500	800	0/8	>800
5	500	0/6		500	0/8	
	1000	0/6	>1000	800	0/8	>800
15	500	0/3		500	0/8	
	1000	1/3	>1000	800	0/8	>800

In the case of oral treatment the compounds of the invention cannot be considered to be toxic on any of the animal species used. The LD_{50} value proved to be higher than 1000 mg/kg on mice and higher than 800 mg/kg on rats. Diminution of the spontaneous motor activity and muscular rigidity were observed on mice whereas a slight increase in the spontaneous motor activity and salivation, decrease in the muscular tone and eventually a ptosis were registered on rats.

It is obvious from the above results that, when given even in a low dose, the compounds of the invention effectively inhibit the spontaneous gastric-acid secretion and, in addition, they exert a strong stomach wall-protecting action. Their therapeutic ratio (safety index) is very favourable. Thus, they may be useful for the treatment of ulcers of the digestive system (stomach and duodenal ulcer).

For the therapeutical use the active compounds of the invention are suitably formulated to pharmaceutical compositions in such a way that, after mixing them with known non-toxic inert solid or liquid carriers, diluting,

binding agents and/or other additives commonly used in the pharmaceutical industry for enteral or parenteral administration, they are transformed to one of the usual drug formulations. Carriers, diluting or binding agents suitable for the above demands are e.g. water, gelatine, lactose, saccharose, starch, pectin, magnesium stearate, stearic acid, talc, various vegetable oils as well as glycols such as propylene glycol or polyethylene glycol. Pharmaceutical additives, auxiliaries are e.g. the preservative agents such as methyl 4-hydroxybenzoate, various native or synthetic emulsifying, dispersing or wetting agents, colouring and flavouring agents, buffer substances as well as agents promoting the disintegration or dissolution, and other substances improving the desired effect.

"Usual drug formulations" are meant to be: oral compositions prepared by using the above-mentioned pharmaceutical additives; these compositions may be solid forms, e.g. tablets, capsules, powders, dragées, pills or granules or liquid forms, e.g. syrups, solutions, emulsions or suspensions; furthermore rectal compositions such as suppositories; as well as parenteral compositions, e.g. injectable solutions and infusions.

The preferable dose of the compounds according to the invention is 1 or 2 tablet(s), capsule(s) or dragée(s) containing 20 mg of the active ingredient each.

The invention also relates to pharmaceutical compositions containing a compound of the general formula (Ia) or (Ib), respectively, or a pharmaceutically acceptable acid-addition salt thereof as active ingredient; as well as to a process for preparing these compositions.

The invention furthermore relates to a method of protecting the gastric mucosa or inhibiting ulcers of the digestive system. This method comprises administering a therapeutically effective amount of an active agent of

the general formula (Ia) or (Ib), respectively, or a pharmaceutically acceptable acid-addition salt thereof to the patient.

The invention is illustrated in detail by the following non-limiting Examples.

The structures of compounds prepared by using the process described in the Examples were proven by ^{1}H- and ^{13}C-NMR spectra, infrared spectra as well as in a number of cases by mass spectra. The signals of NMR spectra are given in ppm according to the scale related to TMS.

R_f values indicated in the Examples were determined by layer chromatography on silica gel (DC-Alufolien Kieselgel 60 F_{254} Merck, Darmstadt) by using the following solvent systems:

A: ethyl acetate/methanol = 8:2

B: ethyl acetate

C: ethyl acetate/methanol = 7:3

D: ethyl acetate/carbon tetrachloride = 1:1

Example 1

Preparation of 3-{[2-(dimethylamino)benzyl]thio}--4,5-dimethyl-1,2,4-triazole dihydrochloride

To a solution containing 7.8 g (60 mmol) of 4,5--dimethyl-1,2,4-triazole-3-thiol (J. Chem. Soc. 1959, page 3799) in 60 ml of dimethylformamide, 12.0 g (60 mmol) of [2-(chloromethyl)phenyl]dimethylammonium chloride (J. Chem. Soc. 1954, page 4127) are added at 40 °C under stirring. The ammonium salt is dissolved under stirring within a few minutes and precipitation occurs from the solution after 10 minutes. After filtering the precipitate is washed 3 times by suspending it in 100 ml of acetone each. The product is dried over phosphorus pentoxide under reduced pressure to obtain the aimed dihydrochloride as white crystals in a yield of 19.8 g (98.5 %), m.p.: 172-175 °C, R_f: 0.5 (A).

Examples 2 to 5

By following the process described in Example 1 above and using the corresponding 1,2,4-triazolethiol as starting substance, the compounds of general formula (Ia) or (Ib), respectively, indicated in Table 8 are obtained. In these compounds R_1 and R_2 are as shown in Table 8 and n is zero.

Table 8

Example No.	General formula	R_1	R_2	M.p.* °C	R_f	Solvent system
2	(Ia)	CH_3		82-84	0.15	B
3	(Ia)		H	194-197	0.7	D
4	(Ia)	H	CH_3	153-155	0.8	C
5	(Ib)	CH_3	CH_3	147-152	0.85	A

* In the Table the melting point of the dihydrochloride salt of the compounds is given.

Example 6

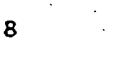
Preparation of 3-{[2-(dimethylamino)benzyl]thio}--4,5-dimethyl-1,2,4-triazole

12.0 g (36 mmol) of dihydrochloride prepared according to Example 1 are portionwise added to a mixture of 250 ml of 5 % aqueous sodium hydrogen carbonate solution and 250 ml of chloroform. After cessation of the effervesence the mixture is shaken and then separated. After extracting the aqueous phase twice with 125 ml of chloroform each, the combined chloroform solution is dried over anhydrous sodium sulfate, then evaporated under reduced pressure. The aimed base is recrystallized from ethanol to give a yield of 9.1 g (97 %), m.p. 54-55 °C, R_f: 0.5 (A). The aimed base forms colourless lamellar crystals.

Examples 7 and 8

By following the procedure described in Example 6 the bases of general formula (Ia) shown in Table 9 are obtained. In these compounds R_1 and R_2 are as given in Table 9 and n is zero.

Table 9

Example No.	R_1	R_2	M.p.* °C	R_f	Solvent system
7	H	CH_3	oil	0.45	A
8	CH_3		130-132	0.15	B

Example 9

Preparation of 3-{[2-(dimethylamino)benzyl]thio}--2-methyl-1,2,4-triazole

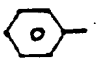
After dissolving 1.76 g (16 mmol) of 2-methyl--1,2,4-triazole-5-thiol [Ann. 643, 121-128 (1961)] in 16 ml of dimethylformamide, 3.2 g (16 mmol) of [2-(chloromethyl)phenyl]dimethylammonium chloride are added at room temperature. The mixture is stirred at room temperature for 2 hours, then evaporated under reduced pressure. The thick oily residue is shaken with a mixture of 100 ml of 5 % aqueous sodium hydrogen carbonate solution and 100 ml of chloroform. The aqueous phase is extracted twice with 50 ml of chloroform each, the organic solution is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product obtained is purified by chromatography on a silica gel column by using ethyl acetate as eluent. After evaporating the fractions containing the aimed compound, a thin oil is obtained in a yield 3.5 g (88 %), R_f: 0.7 (B).

Examples 10 to 14

By following the process described in Example 9 and using the corresponding 1,2,4-triazolethiol as starting

substance the compounds of general formula (Ia) shown in Table 10 are obtained. In these compounds R_1 and R_2 are as given in Table 10 and n is zero.

Table 10

Example No.	R_1	R_2	M.p. °C	R_f	Solvent system
10	CH_3	H	104-108	0.3	B
11	H	H	48-52	0.25	B
12	H		79-83	0.25	D
13		CH_3	57-59	0.5	B
14	H_3CO- 	CH_3	52-56	0.4	B

Example 15

Preparation of 3-{[2-(dimethylamino)benzyl]-sulfinyl}-4,5-dimethyl-1,2,4-triazole

Method a)

10.0 g (30 mmol) of the compound prepared according to Example 1 are transformed to the free base by a mixture of 240 ml of 5 % aqueous sodium hydrogen carbonate solution and 240 ml of chloroform as described in Example 6. The chloroform solution is dried, supplemented to 1200 ml with anhydrous chloroform and then 12.0 g (33 mmol) of 55 % 3-chloroperbenzoic acid are portionwise added to the obtained solution at 25 °C under stirring. After stirring for further 2 hours the reaction mixture is washed 3 times with 300 ml of 5 % aqueous sodium hydrogen carbonate solution each. The chloroform solution is dried over anhydrous sodium sulfate and evaporated. The residue is subjected to chromatography on a silica gel column by using ethyl acetate first and then a 8:2 mixture of ethyl

acetate and methanol as eluent. After evaporating the fractions containing the aimed compound, a yellow oily residue is obtained in a yield of 2.5 g (30.1 %), R_f: 0.4 (A).

Method b)

3.50 g (15 mmol) of 3-{[2-(dimethylamino)benzyl]--thio}-4,5-dimethyl-1,2,4-triazole dihydrochloride salt (see Example 1) are added in small portions to a mixture containing 120 ml of 5 % aqueous sodium hydrogen carbonate solution and 120 ml of chloroform under stirring. After separation the aqueous phase is extracted twice with 60 ml of chloroform each. The chloroform solution is filled up to 600 ml with chloroform and 8.0 g (22 mmol) of 55 % 3-chloroperbenzoic acid are added in one portion. After 3 minutes following the dissolution of perbenzoic acid the reaction mixture is washed 3 times with 50 ml of water each and the chloroform phase is set aside. 1.9 g (15 mmol) of sodium sulfite are dissolved in 50 ml of water and 15 ml of 2 N (30 mmol) hydrochloric acid are added. The solution smelling of sulfur dioxide is immediately dropwise added to the previously separated aqueous phase during about 5 minutes at room temperature. The pH value of the intensely yellow solution is adjusted from 1 to a value of 7 to 8 by adding 5 % aqueous sodium hydrogen carbonate solution. The mixture is extracted 3 times with sodium hydrogen carbonate solution, then the mixture is extracted 3 times with 120 ml of chloroform each. The chloroform phases are combined with the chloroform phase previously set aside, cautiously shaken once with 20 ml of water, dried over anhydrous sodium sulfate and evaporated. The residue is crystallized from ethyl acetate, filtered and dried on air to give the aimed product in a yield of 2.4 g (57 %), m.p.: 104-106 °C.

Examples 16 and 17

By following the process described in Example 15, Method a) or b), compounds of general formulae (Ia) and (Ib) shown in Table 11 are obtained. In these compounds R_1, R_2 and n are as given in Table 11.

Table 11

Example No.	General formula	R_1	R_2	n	M.p. °C	R_f	Solvent system	Method
16	(Ia)	CH_3		2	145-148	0.6	B	a)
17	(Ib)	CH_3	CH_3	1	oil	0.3	B	a) or b), resp.

Example 18

Preparation of 3-{[2-(dimethylamino)benzyl]-sulfinyl}-2-methyl-1,2,4-triazole

Method a)

After dissolving 7.0 g (28 mmol) of the compound prepared according to Example 9 in 850 ml of methylene chloride, 9.6 g (31 mmol) of 55 % 3-chloroperbenzoic acid are added at 25 °C under stirring. After 30 minutes the reaction mixture is washed 3 times with 250 ml of 5 % aqueous sodium hydrogen carbonate solution each, then dried over anhydrous sodium sulfate. After evaporating the organic solution under reduced pressure, the oily residue is subjected to chromatography on silica gel by using ethyl acetate as eluent. After evaporating the fractions containing the aimed compounds an oily residue is obtained in a yield of 1.5 g (20.2 %), R_f: 0.45 (B).

Method b)

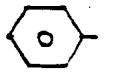
After dissolving 3.75 g (15 mmol) of the compound prepared according to Example 9 in 600 ml of chloroform, 6.0 ml (27 mmol) of 78 % 3-chloroperbenzoic acid are added at 25 °C. After vigorously stirring the reaction

mixture for 5 minutes, 56 ml of 5 % aqueous sodium hydrogen carbonate solution (33 mmol) are added, then the two-phase mixture is vigorously stirred for additional 5 minutes. Simultaneously, 4.5 g (35 mmol) of sodium sulfite are dissolved in 50 ml of water, 36 ml of 2 N (72 mmol) hydrochloric acid are dissolved in 50 ml of water, 36 ml of 2 N (72 mmol) hydrochloric acid are added and the thus-prepared sulfurous acid solution is quickly dropped to the above reaction mixture. The yellow heterogeneous reaction mixture is vigorously stirred for 5 minutes, then, after separating the two phases, the chloroform phase is washed 3 times with 120 ml of 5 % sodium hydrogen carbonate solution each. The aimed product is obtained by using the procedure described under Method a) of Example 18. A yield of 1.2 g (32 %) is obtained.

Examples 19 to 24

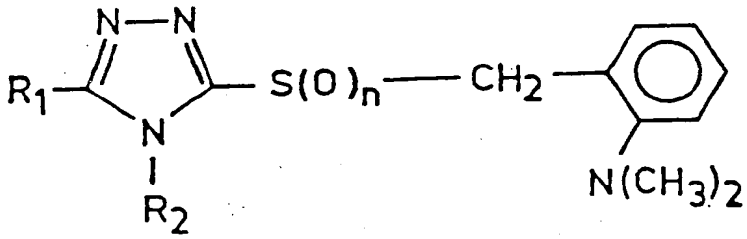
By following the procedure described in Example 18 compounds of general formula (Ia) shown in Table 12 are obtained. In these compounds R_1, R_2 and n are as given in Table 12.

Table 12

Example No.	R_1	R_2	n	M.p. °C	R_f	Solvent system	Method
19	CH_3	H	1	94- 96	0.2	B	a) or b), resp.
20	H	H	1	143-146	0.1	B	a) or b), resp.
21	H	CH_3	1	oil	0.35	A	a) or b), resp.
22		CH_3	1	121-124	0.45	B	a) or b), resp.
23	H_3CO- 	CH_3	2	165-168	0.9	C	a)
24	H_3CO- 	CH_3	1	oil	0.65	C	b)

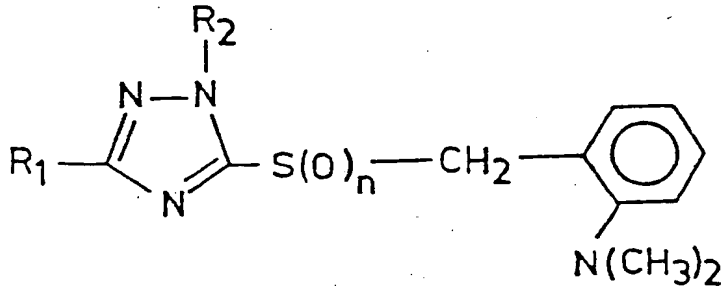
Claims

1. 1,2,4-Triazole derivatives of the general formulae (Ia)



(Ia)

and (Ib),



(Ib)

wherein

R_1 and R_2, which are the same or different, stand for hydrogen; C_{1-4} alkyl or C_{1-4} alkenyl group; or a phenyl group optionally substituted by C_{1-4} alkyl or alkoxy group; and

n is 0, 1 or 2,

and acid addition salts of these compounds.

2. A compound selected from the group consisting of 3-{[2-(dimethylamino)benzyl]thio}-4,5-dimethyl--1,2,4-triazole,

3-{[2-(dimethylamino)benzyl]sulfinyl}-4,5-dimethyl--1,2,4-triazole,

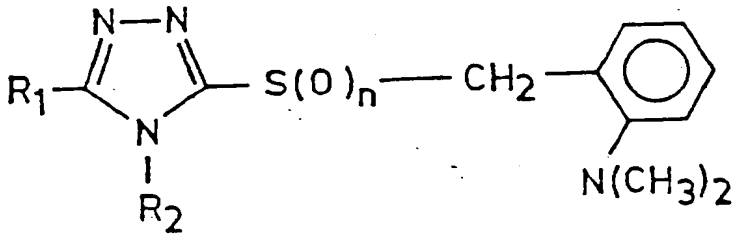
3-{[2-(dimethylamino)benzyl]thio}-2-methyl-1,2,4--triazole,

3-{[2-(dimethylamino)benzyl]thio}-2,5-dimethyl--1,2,4-triazole

and the acid addition salts of these compounds.

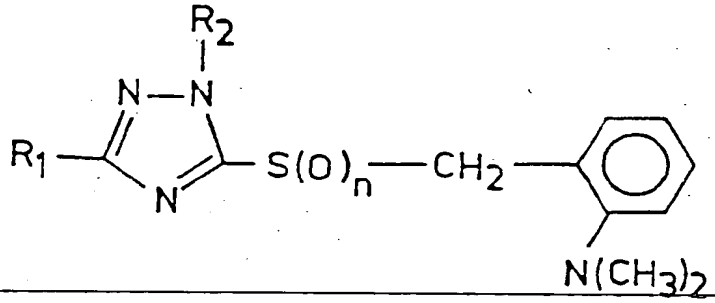
3. A pharmaceutical composition, which comprises as active ingredient a novel 1,2,4-triazole derivative of general formula (Ia) or (Ib), respectively, wherein R_1, R_2 and n are as defined in claim 1, or a pharmaceutically acceptable acid-addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

4. A process for the preparation of novel 1,2,4-triazole derivatives of general formulae (Ia)



(Ia)

and (Ib),



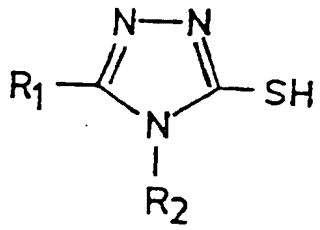
(Ib)

wherein

R_1 and R_2, which are the same or different, stand for hydrogen; C_{1-4} alkyl or C_{1-4} alkenyl group; or a phenyl group optionally substituted by C_{1-4} alkyl or alkoxy group; and

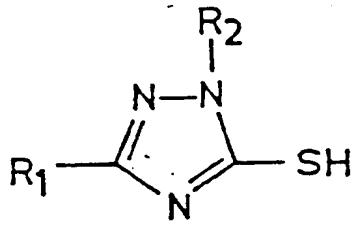
n is 0, 1 or 2,

and acid addition salts of these compounds, which comprises reacting a compound of general formula (IIa)



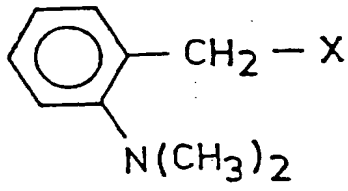
(IIa)

or (IIb),



(IIb)

respectively, wherein R_1 and R_2 are as defined above, or a tautomer thereof with a compound of general formula (III),



(III)

wherein X means a leaving group, or with an acid-addition salt thereof and, if desired, transforming the obtained compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is zero, to a compound of general formula (Ia) or (Ib), respectively, wherein R_1 and R_2 are as defined above and n is 1 or 2, by oxidation and optionally by subsequent reduction and/or converting an obtained base to an acid-addition salt by using an organic or inorganic acid or converting an obtained salt to the corresponding free base.

5. A process as claimed in claim 4, which comprises reacting the compound of general formula (III) in the form of one of its acid-addition salts.

6. A process as claimed in claim 4 or 5, which comprises reacting the compound of general formula (IIa) or (IIb), respectively, or a tautomer thereof with the compound of general formula (III) or an acid-addition salt thereof in a dipolar aprotic solvent.

7. A process as claimed in claim 6, which comprises using dimethylformamide, dimethylacetamid or dimethylsulfoxide as solvent.

8. A process as claimed in any of claims 4 to 7, which comprises carrying out the oxidation with 3-chloroperbenzoic acid in a halogenated hydrocarbon.

9. A process for the preparation of a pharmaceutical composition, which comprises mixing as active ingredient a novel 1,2,4-triazole derivative of the general formula (Ia) or (Ib), respectively, wherein R_1, R_2 and n are as defined in claim 4, or a pharmaceutically acceptable acid-addition salt thereof, prepared by using the process claimed in claim 4, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

10. A method for protecting the gastric mucosa and inhibiting the ulcers of the digestive system, characterized by administering to a patient to be treated a therapeutically effective amount of an 1,2,4-triazole derivative of the formula (Ia) or (Ib), respectively, wherein R_1, R_2 and n are as defined in claim 1, or a pharmaceutically acceptable acid-addition salt thereof alone or in the form of a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00063

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 249/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 249/12, 233/84; A 61 K 31/41

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chemical Abstracts (Columbus, Ohio, USA) AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0 354 788 (NIPPON CHEMIPHAR CO) 14 February 1990 (14.02.90), claim 1; page 6, lines 1-50.	1,4-6
A	Chemical Abstracts, Vol. 114, No.3, issued 1991, January 21 (Columbus, OHIO, USA), Honma, Yasushi et al. "Preparation of imidazole derivatives as antiulcer agents." Page 709, column 2, the abstract no. 23 964d. Jpn. Kokai Tokkyo Koho JP 02 49,727 (90 49,727).	1,4
A	Chemical Abstracts, Vol. 116, No.5, issued 1992, February 03 (Columbus, OHIO, USA), Yamakawa, Tomio et al. "Synthesis and structure-activity relationships of N-substituted 2-((2-imidazolylsulfinyl)methyl)anilines as a new class of gastric hydrogen/potassium ion-ATPase inhibitors." Page 18, column 1, the abstract no. 33 918x. Chem. Pharm. Bull. 1991, 39(7), 1746-52.	1,9,10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 June 1994 (01.06.94)	21 June 1994 (21.06.94)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer e.h. Telephone No. 1/5337058/44

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00063

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 10 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 93/00063

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 354788	14-02-90	JP A2 2138263	28-05-90
		AU A1 39461/89	15-02-90
		AU B2 624406	11-06-92
		DK A0 3928/89	10-08-89
		DK A 3928/89	11-02-90
		US A 5082943	21-01-92
		US A 5180836	19-01-93
		ZA A 8906065	30-05-90